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Letter to the Editor

Temsirolimus: Is Improved Survival the Correct Expression of Drug Activity?

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We read with great interest the U.S. Food and Drug Administration approval summary of temsirolimus by Kwitkowski et al. [1], published in ***The Oncologist*** online on March 23, 2010. In the introduction, there is a fascinating insight into the most recent therapeutic achievements concerning kidney cancer, with a detailed analysis of some weaknesses concerning the registration studies of sorafenib and sunitinib; in particular, the lack of benefits in terms of overall survival was underlined.

Nevertheless, the rigorous analysis of data seems to be missed when the authors discuss the efficacy endpoints of the temsirolimus registration study. Temsirolimus was studied in a three-arm phase III trial [2], in which the control arm was interferon-α and the experimental arms were temsirolimus alone or temsirolimus plus interferon-α. Only poor-risk patients were enrolled with a performance status score (Karnofsky) inferior to 80%. Overall survival was the primary endpoint. The authors underlined that temsirolimus alone showed a benefit in terms of overall survival when compared with interferon-α alone (10.9 months versus 7.3 months; $p = .008$). The authors also highlighted a statistically significant benefit in terms of progression-free survival (PFS). Indeed, according to the independent reviewers' analysis, the PFS times were 3.1 months, 5.5 months, and 4.7 months for interferon-α, temsirolimus, and combination therapy, respectively, without a statistically significant difference [2, 3]. A statistically significant difference was found only when investigators' evaluations were considered; the PFS intervals were 1.9 months, 3.8 months, and 3.7 months for interferon-α, temsirolimus, and combination therapy, respectively, with $p = .0001$ in favor of temsirolimus when compared with interferon-α [4]. The PFS interval as assessed by site investigators was shorter because, according to the personal clinical judgment of clinicians before the scheduled radiological assessment, clinical signs of progressive disease were present. The authors of the present review did not mention the differences in PFS times between external reviewers' and site investigators' assessments.

This issue is, without uncertainty, a very important one, because temsirolimus is the first cancer drug showing a benefit in terms of survival, not accompanied by a benefit in terms of PFS. Indeed, in oncological trials, the correlation between longer survival and longer PFS times is so strong that PFS is often considered a surrogate endpoint for survival [5].

In fact, the way in which this benefit in terms of survival is achieved should be further investigated. We wonder whether the benefit in terms of survival is a result of drug activity or a consequence of a detrimental effect on survival of interferon-α in this subset of poor-risk patients. The low tolerability for interferon in patients with

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a poor performance status is a known limitation to the use of this drug [6, 7].

In this regard, we wonder again whether the presence of interferon in the combination arm of the study could be responsible for the worse outcome, as Hudes at al. [2] suggested in the discussion of their paper. Finally, reporting the issue of the efficacy of temsirolimus in terms of PFS as well might contribute to overestimating its real effectiveness, because further studies are needed to comprehend its benefits in selected patients. Interestingly enough, a retrospective analysis of patients with papillary or chromophobe histology in the same phase III study showed a significantly longer overall survival time when compared with the whole population [8].

However, apart from these personal observations, in our opinion, the differences in terms of PFS intervals between investigators' and independent reviewers' assessments should have been clearly stated in the paper.

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